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Bone and Bone Graft Healing

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Bone is unique in connective tissue healing because it heals entirely by cellular regeneration and the production of a mineral matrix rather than just collagen deposition known as scar. This article discusses the cellular, tissue, and organ levels in each of the following sections—skeletal embryology, normal bone, examples of abnormal bone, and bone graft healing—as they relate to the jaws and the craniofacial skeleton.

Pertinent embryology of the skull, facial bones, and jaws

The calvarium, facial bones, clavicle, and jaws are intramembranous bones that arise from cells that migrated from the neural crest adjacent to the notochord. These bones develop, grow, and heal by direct ossification of mesenchyme rather than from preformed cartilage. By contrast, all the other bones of the skeleton, which are referred to as the appendicular skeleton, arise from preformed cartilage by the process known as endochondral ossification. Specifically, the calvarium originates as six membrane-covered neural crest cell islands that correspond to the bilateral frontal bone segments, the bilateral parietal bone segments, and the midline occipital squamous plate and occipital bone proper separated by fontanelles [1]. The anterior fontanelle closes at approximately 1.5 years of age and becomes known as the midsagittal suture. The maxilla as well as the incus and mandible arise separately from the first pharyngeal arch. Although each arises with a central cartilage element, which in the maxilla is called the palatopterygoquadrate bar and in the mandible is called Meckle's cartilage, the cartilage itself does not transform into bone but only serves as a scaffold on which neural crest mesenchyme transforms into bone. These cartilages involute before birth. The bones of the calvarium, facial bones, jaws, and even the clavicle have been referred to as "ectomesenchymal bone" and are thought to be embryologically similar. Bone morphogenetic protein-4 (BMP-4) also is thought to play the major role in neural crest migration orientation and actual bone morphogenesis, whereas BMP-2 plays a major role in neural crest ventralization toward the jaws and away from the calvarium but less of a role in actual bone development [2].

The conjectured and unproven importance of this embryology is that bone grafts from the calvarium are ideally suited for midface and jaw reconstruction where feasible because they are similar ectomesenchymal bones. This is reinforced by the frequent observation that calvarial block onlay grafts to the midface and jaws experience less resorption than do grafts from endochondral bones, such as the ilium or ribs. The disease of myositis ossificans also has been shown to relate to muscles that overexpress receptors for BMP-4 [2]. It has also been suggested that a recombinant human BMP-4 may be the most ideal recombinant BMP for jaw and facial bone reconstruction.

Bone as a tissue

Bone is fundamentally composed of cells, inorganic matrix, and organic matrix. The cells are hematopoietic (blood forming) and nonhematopoietic (non–blood forming) stem cells in the bone marrow, osteoblasts (of which some are endosteal osteoblasts that line the trabecular bone between the cortices (Fig. 1) and others

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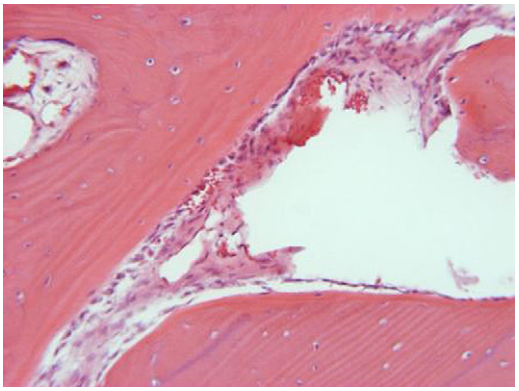

Fig. 1. Endosteal osteoblasts lining trabecular bone.

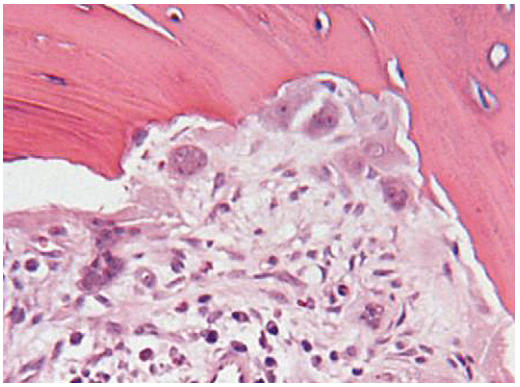

Fig. 3. Osteocytes are seen here in their lacunae. Osteoclasts are resorbing bone as multinucleated giant cells.

that line the inner surface of each cortex), and some other osteoblasts that comprise the inner or cambium layer of the periosteum (Fig. 2). Osteocytes, which are mature osteoblasts encased in a mineral matrix, and osteoclasts, which resorb bone upon stimulation and begin the bone renewal process, which is often termed "bone turnover" or "bone remodeling," are the remaining bone cells (Fig. 3). The inorganic matrix and organic matrix are combined. The basic organic component is type 1 collagen, which comprises 98.5% of the noncellular organic matrix. The inorganic matrix is nearly all hydroxyapatite. Essentially, bone matrix is mostly type 1 collagen laced with crystals of hydroxyapatite. However, there are several important noncollagen proteins in bone, namely BMP, insulin-like growth factors-1 and -2 (IGF-1 and IGF-2), sialoprotein, and osteopontin.

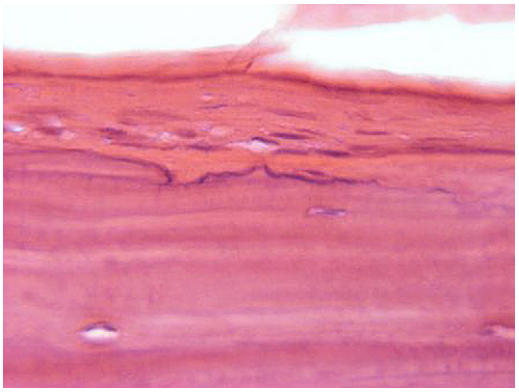

Fig. 2. Periosteum with several cell layers of osteoblasts. The inner-most layer is known as the cambium layer.

The evolutionary purpose of bone as a tissue and the skeleton as a whole is internal structural integrity, an attachment for muscles, a reservoir for hematopoietic and mesenchymal stem cells, and a main regulator of serum calcium for skeletal and cardiac muscle contraction and therefore locomotion and organ perfusion.

Bone renewal (remodeling)

The biochemistry of bone as a tissue can best be explained in the context of bone cell interactions starting with existing bone. Bone is normally inhibited from resorption by osteoprotegerin (OPG), which is a protein secreted by osteoblasts to regulate the rate of resorption as an inhibitory signal to the osteoclast (Fig. 4) [3]. As the osteoblast matures into an osteocyte it gradually loses its ability to secrete OPG and becomes vulnerable to normal osteoclastic resorption. Therefore, old bone, injured bone, and dead bone become resorbed.

Osteoclasts arise from mononuclear precursor cells of the macrophage linage in bone marrow [4]. They mature rapidly under the stimulation of macrophage colony stimulating factor and interleukin-1 and -6 (IL-1 and IL-6) and are then extruded into the circulation as quiescent nonresorbing osteoclasts because of the inhibiting influence of circulating calcitonin (Fig. 5). The osteoclast only begins active bone resorption in response to the overriding signal of circulating parathyroid hormone and locally secreted receptor activator nuclear kappa-b ligand (RANKL) [5,6]. RANKL binds to RANK receptors on the osteoclast cell membrane to initiate resorption [7]. Although RANKL is known to be secreted

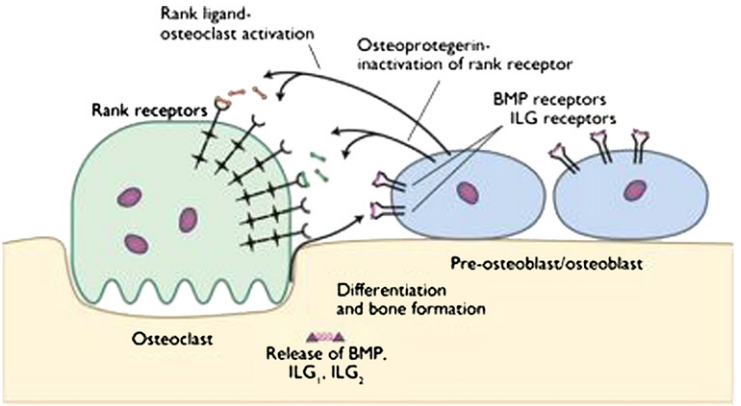

Fig. 4. Osteoblasts secrete OPG, which is a competitive receptor site binder to RANKL for the RANK receptor on osteoclasts. Its effect is to keep osteoclasts inactive and inhibit bone resorption.

by cancers to create pathologic cavities in bone [8], it is also secreted by normal osteoblasts to increase bone resorption (see Fig. 4). Normal osteoblasts also secrete OPGs as a false ligand that competes with RANKL to inhibit bone resorption by occupying the RANK receptor on the osteoclast cell membrane. This gives the osteoblast up-regulation and down-regulation control of the osteoclast and either limits the rate and amount of local bone resorption or increases it (see Fig. 4).

Osteoclast-mediated normal bone resorption begins the bone renewal/bone turnover process. The activated osteoclast adheres to a bone surface and develops a ruffled border against the bone surface as it seals the edges and forms a Howship's lacuna (Fig. 6). The osteoclast then secretes hydrochloric acid to dissolve the inorganic matrix and several collagenases to break down the organic matrix (Fig. 7). Several osteoclasts commonly work together to excavate a larger area of old bone, which is referred to as a cutting cone (Fig. 8).

Because BMP and IGF-1 and -2 are acid insoluble, they are released during bone resorption and remain as active cytokines. These released cytokines (growth and differentiation factors) bind to the cell membrane surfaces of local stem cells and somewhat to circulating stem cells to induce a differentiation into osteoblasts, and then further stimulates them to secrete osteoid. A cutting cone headed by resorbing osteoclasts and followed by a trial of osteoblasts secreting osteoid is known as a bone metabolic unit (BMU) (Fig. 9). Osteoclasts are known to live for only 14 days; newly activated osteoclasts are needed to sustain the BMU which continues for 150 to 180 days. This lifespan of the BMU is known as a sigma, and it relates that in homeostasis some bone replaces itself twice each year or at a rate of 0.5% per day.

So now bone has come full circle. The balance of bone apposition and bone resorption once again comes under the influence of the osteoblast. The young osteoblast secretes OPG as a false

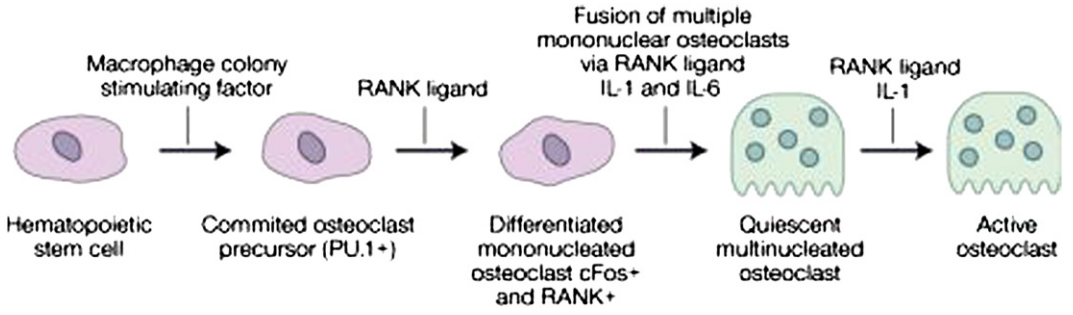

Fig. 5. Osteoclast lineage from marrow monocytes to activated osteoclasts.

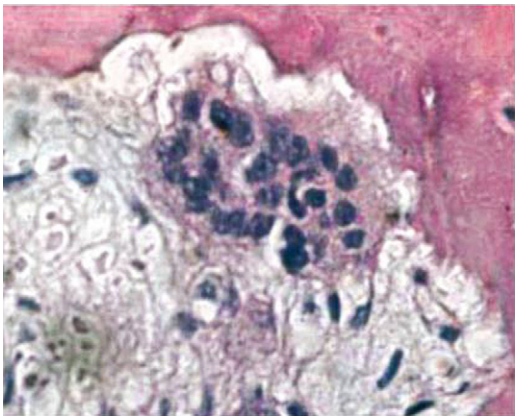

Fig. 6. Osteoclasts resorbing bone in excavation cavity known as a Howship's lacunae.

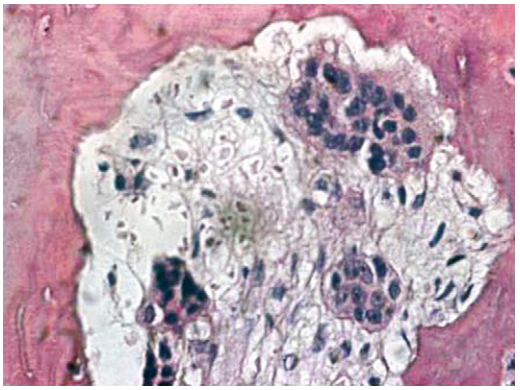

Fig. 8. Several osteoclasts work together to excavate a tunnel through bone, which is known as a cutting cone.

ligand to the RANK receptor on the osteoclast, which by competitive inhibition outpaces RANKL, so that the bone is maintained until this balance tips in the favor of RANKL by either the aging of the osteocyte (old age) or by disease so that the process begins once again. As two BMUs form new bone, they come in contact with one another and must osseointegrate to make the bone a single coalescent tissue rather than a set of mobile pieces. This is histologically seen as a cementing line (also called resting line or reversal line by some). The cementing substance is composed of sialoprotein and osteopontin, which bind two bone-forming areas together (Fig. 10). As these proteins harden by cross-linking and the collagen strands from each bone surface become incorporated into this cement substance—much in the same manner as reinforcement bars are placed into cement pillars during highway construction—the two BMUs become bound together.

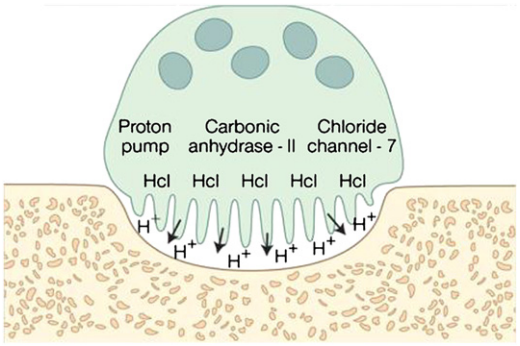

Fig. 7. Osteoclasts resorb bone via HCL and collagenase. They have three main mechanisms to produce hydrochloric acid.

Examples of abnormal bone

The knowledge of this bone physiology helps us understand the pathology of cancer metastasis, osteoporosis, osteopetrosis, and the toxic effects of bisphosphonates on normal bone.

Cancer-induced bone resorption

Most cancers are incapable of bone resorption. Instead, they secrete RANKL to activate normal osteoclasts to resorb bone and create bony cavities into which they proliferate (Fig. 11). This is their basis for bony invasion and their metastasis to

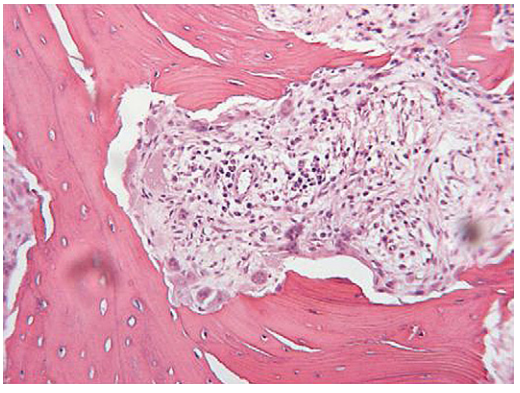

Fig. 9. A bone metabolic unit (BMU) is formed when osteoclasts resorb bone and liberate bone-inductive proteins to cause osteoblast differentiation and new bone formation.

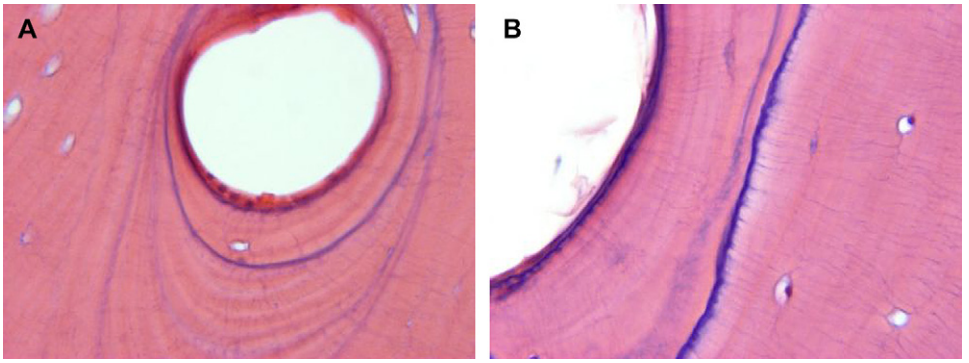

Fig. 10. (*A, B*) Low and high power cementing lines as seen here are approximately 5 μm thick and are composed of osteopontin and sialoprotein.

bone. In an effort to halt this cancer-stimulated bone resorption, the intravenous nitrogen-containing bisphosphonates pamidronate (Aredia) and zoledronate (Zometa) were synthesized. These drugs and all nitrogen-containing bisphosphonates are potently toxic to the osteoclast so as to cause their death and population depletion (Fig. 12). By doing so, the cancer cannot resorb bone and small metastatic cancer deposits are held in check. As our profession has learned, however, repetitive doses accumulate in bone, particularly bones of more active remodeling, most notably the alveolar bone of the jaws [9,10], which results in a halt to local bone renewal and osteonecrosis (Fig. 13).

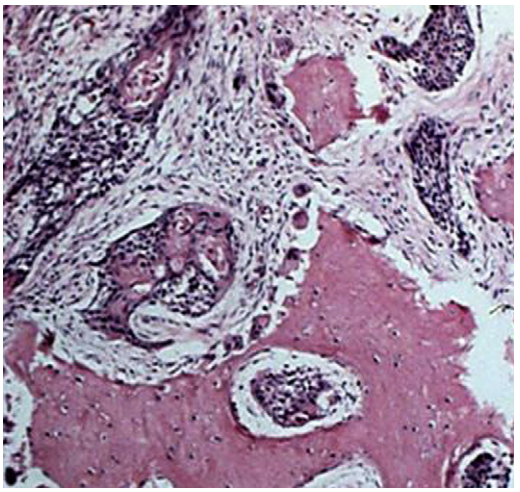

Fig. 11. Cancers resorb bone through their secretion of RANKL, which activates osteoclasts to resorb cavities in bone, into which the cancer proliferates. Here, osteoclasts are seen to be resorbing bone with the cancer cells at a distance from the bone surface.

Osteoporosis and bisphosphonates

In a similar effort to slow or halt age- and menopause-related bone resorption leading to osteoporosis, the oral bisphosphonates residronate (Actonel), alendronate (Fosamax), and ibandronate (Boniva) have been used. Their toxic effects on the osteoclast are designed to retain existing bone and allow it to increase its mineralization as measured by bone density tests and prevent osteoporosis-related fractures [11,12]. Toxicity to the osteoclast prevents resorption, which is needed to renew bone; therefore, old and more brittle bone accumulates over the years. Although they initially increase the strength of bone by further mineralization, over many years the unrenewed bone becomes more brittle, which limits its fracture prevention [13,14] and increases the risk for osteonecrosis in the jaws [15].

Osteopetrosis

Nearly identical to the pathophysiology of bisphosphonate-induced osteonecrosis is the disease of osteopetrosis. This disease of eight genetic variants, all of which render the osteoclast nonfunctional or absent, also results in necrotic bone in the jaws caused by reduced or absent bone renewal (Fig. 14). Toward the other extreme, overfunction of the osteoclast—as seen in untreated primary hyperparathyroidism—results in resorption cavities known as brown tumors and in hypercalcemia, which results in depolarized nerves and muscles causing mental confusion, abdominal pains, constipation, and weakness, the classic symptoms of primary hyperparathyroidism.

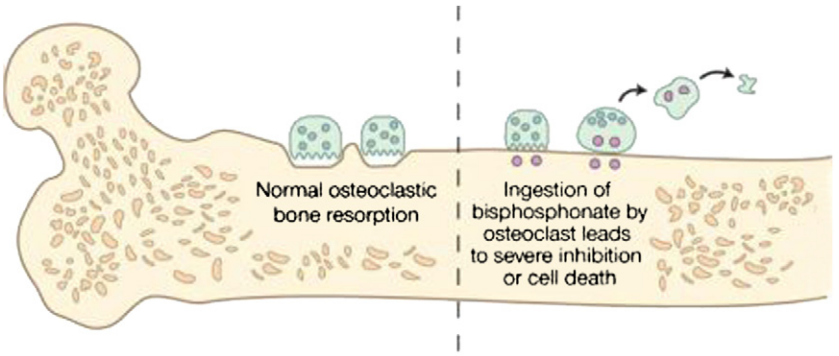

Fig. 12. Bisphosphonates cause rapid osteoclastic death by inhibiting enzymes in the mevalonate branch pathways which prevents bone renewal.

The structure of bone

The histology of bone begins with Haversian systems, which are the trademark of mature bone. Haversian systems are concentric rings of interconnecting osteocytes surrounding a Haversian canal (Fig. 15). Haversian canals are channels through which arterioles, venules, and lymphatics pass. The bony surface of the canal is lined by endosteal osteoblasts, which usually can be seen to have formed a ring of osteoid against the mature bone. Haversian canals are connected at right angles to other Haversian canals by similar but smaller diameter canals, known as a Volkmann canal. Because Haversian systems are concentric circles, they do not geometrically join. Instead, they are joined by mature bone not organized into Haversian systems but organized with lamellar bone and joined to the Haversian system by a cementing line. This area is known as interstitial lamella (Fig. 16).

In long bones, most of the shaft is composed of cortical bone organized into Haversian systems and interstitial lamella. The inner cortical surface is lined by endosteal osteoblasts and the outer cortical surface by periosteal osteoblasts. The bone marrow in the mid-shaft is mostly cellular marrow without much stroma. The adult marrow in the proximal and distant ends of long bones, the vertebrae, the pelvic bones, and craniofacial skeleton is trabecular bone with interconnections. In between, hematopoietic marrow and stem cells reside but are replaced with fibro-fatty marrow as an individual ages. Each trabecula is lined by endosteal osteoblasts and contains osteoid and lamellar bone, some of which may be organized into Haversian systems.

The importance of this knowledge is the recognition that mature bone is viable, vascular, and yet more mineral dense (Fig. 17). This type of bone results in the best primary stability for dental implants. Immature bone can be recognized

Fig. 13. Bisphosphonate-induced osteonecrosis of the jaws.

Fig. 14. Osteopetrosis, a genetic absence of osteoclasts, produces exposed necrotic bone in the jaws identical to bisphosphonate-induced osteonecrosis.

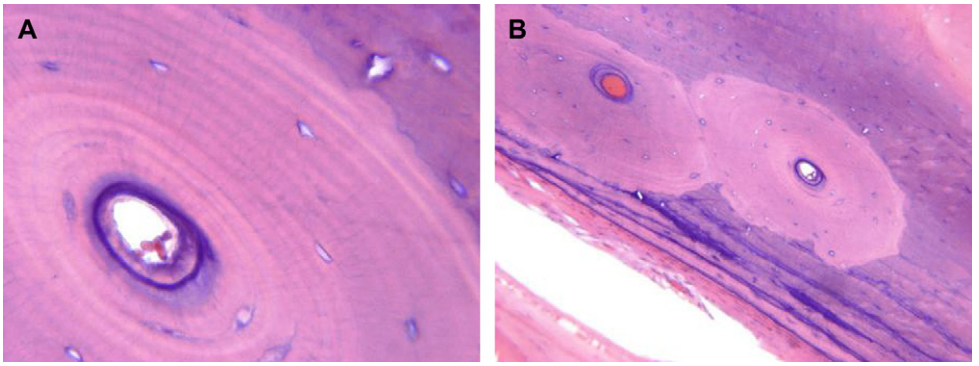

Fig. 15. (*A*) Haversian canal and Haversian system in mature bone. (*B*) Haversian canal and Haversian systems together with interstitial lamella.

histologically as much more cellular, with plump osteocytes in larger lacuna and little or no lamellar architecture (Fig. 18).

Mechanism of bone regeneration and healing

Bone grafts of any type can only regenerate bone through three possible mechanisms: direct osteogenesis, osteoconduction, and osteoinduction. Grafts may develop bone from one, two, or all three of these mechanisms to varying degrees.

Direct osteogenesis

Direct osteogenesis is the formation of osteoid by osteoblasts. Osteogenesis may occur in children without any grafting and has been termed "spontaneous osteogenesis." In these cases, the bone forms from the surrounding periosteum and from the endosteum of adjacent bone. Osteogenesis from a bone graft is often termed "transplanted osteogenesis." In these cases, numerous surviving endosteal osteoblasts—mainly from cancellous marrow because of its extended surface area and marrow stem cells—are the cellular sources of new bone formation. Autogenous cancellous marrow grafts are examples of direct transplanted osteogenesis, which migrates through the blood clot of the wound.

Osteoconduction

Osteoconduction is the formation of new bone from adjacent bone or from periosteum through a matrix that acts as a scaffold. In these cases, the matrix must bind the cell adhesion molecules fibrin, fibronectin, and vitronectin or consist of collagen itself. The natural healing of a tooth socket is an example of osteoconduction, as is

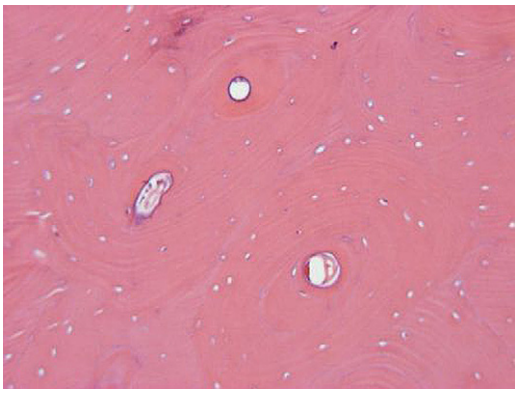

Fig. 16. Lamellar bone between Haversian systems is termed interstitial lamella.

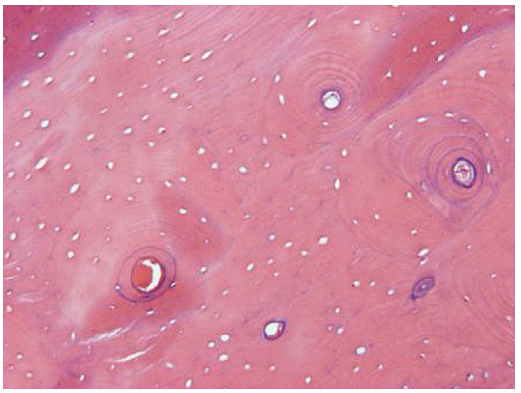

Fig. 17. Mature bone has lamellar architecture, Haversian systems, and a greater mineral density.

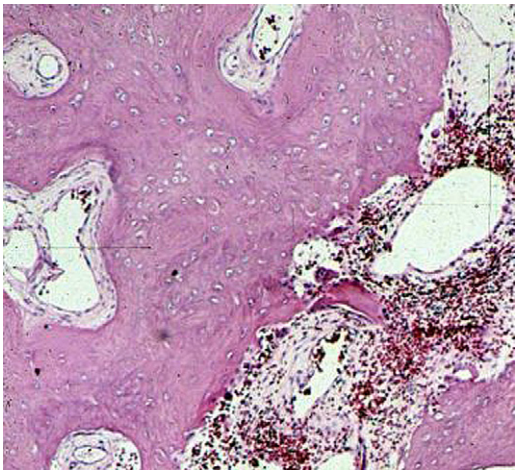

Fig. 18. Immature bone is more cellular, with larger lacunae and sparse or lamellar architecture.

a sinus augmentation graft using a nonviable graft material.

Osteoinduction

Osteoinduction is the formation of bone by the biochemical transformation and stimulation of stem cells into bone-producing cells. BMP, whether endogenous or exogenous, is the best-known bone-inducing agent.

Autogenous bone graft healing

Bone grafts harvested from the craniofacial skeleton versus bone graft harvested from the axial skeleton

The jaws, facial bones, and calvarium arise from embryonic stem cells from neural crest origin. There is a common notion that embryologically derived similar bone grafts from the calvarium perform better than bone grafts from embryologically dissimilar bone grafts harvested from long bones. Although this notion is not confirmed, experienced surgeons who have accomplished both types of grafts have noted that calvarial block grafts to the jaws experience less resorption and volume loss than similar block grafts from the ilium or ribs. This occurrence may be caused by the similarity in the residing stem cells in each bone or to similar architecture. It also may be caused by diplopic vascular channels in calvarial bone that evolved to vent heat from the human brain. This competing theory postulates that this greater number of vascular channels contains more endosteal osteoblasts and stem cells for bone regeneration while promoting an earlier revascularization. In either case, calvarial bone is preferred for grafting the midface, nasal area, and orbits and is used for larger sized maxillary and mandibular ridge augmentations where possible and practical to harvest (Figs. 19–21).

Healing and incorporation of nonvascularized block bone grafts

The mechanisms of healing and incorporation of autogenous block bone grafts are universal regardless of the donor site. The rate of this healing and the amount of final bone formation vary with the donor site, however, and depend on several other factors. The most important factors are the amount of cellular marrow transplanted with the bone graft, the vascularity of the tissue bed, and the attainment of graft stability.

The osteocytes within these grafts die off because of their encasement in a mineral matrix and disruption of their delicate canalicular blood supply. New bone is formed by osteogenesis as a result of surviving endosteal osteoblasts and marrow stem cells, which are few in block grafts, and by osteoinduction from the release of BMP and IGF-1 and -2 as the mineral matrix is resorbed and by osteoconduction through the framework of the graft itself. Block bone grafts form new bone, mostly by osteoinduction and osteoconduction from the adjacent bone margins and much less through direct osteogenesis from surviving osteocompetent cells. This is why larger block grafts form less bone and experience a reduction in their volume when used as onlay grafts. It is also why in

Fig. 19. Cranial bone grafts are best harvested from the parietal bone area because of a greater thickness of bone between the outer and inner table in that area.

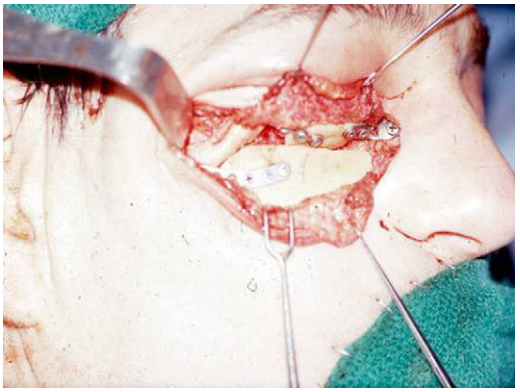

Fig. 20. Cranial bone has a contour similar to the midface and orbital areas and is similar to intramembranous bone.

larger mandibular continuity defects block grafts are noted to show bone regeneration at each resection margin, which tapers to the center, where a residual defect may continue (Fig. 22).

Healing and incorporation of vascularized block grafts

Block grafts on a vascular pedicle, such as a free microvascular fibula, transfer preformed mature bone. In this case, the composite of mature osteocytes, periosteum, and mineral matrix can be transferred in a viable state. Conceptually this would seem the ideal graft and is embraced by many surgeons who are not as familiar with jaw morphology, function, and the need for denture wearing as oral and maxillofacial surgeons. The problem with such preformed bone is more practical than biologic. That is, the fibula is far too small and too straight to be an adequate jaw reconstruction, particularly for the mandible. A fibula is only 10 to 12 mm in height, which is the size of each person's index finger. Placed next to a mandible, the size discrepancy becomes readily apparent. To curve such a straight and brittle cortical bone about the arch form of the mandible also requires two osteotomies. At best, it only reconstructs a small broken jaw, which is not ideal (Fig. 23).

The healing of this type of graft to the host bone is identical to fracture healing, which is via the proliferation of endosteal osteoblasts and periosteal osteoblasts through the fibrin and fibronectin of the blood clot between the bone ends. This process begins with the degranulation of platelets, which cause the migration, differentiation, and stimulation to form a bony callus. The initial internal and external callus first

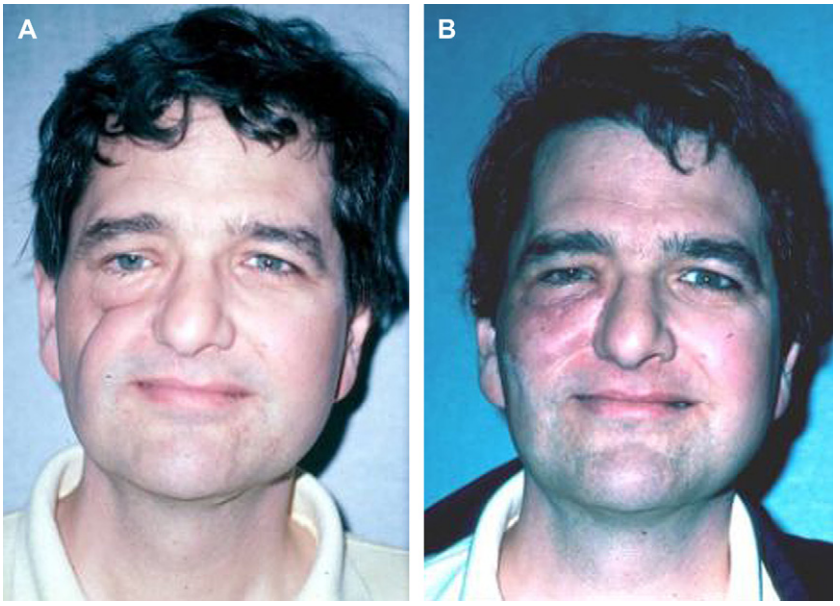

Fig. 21. (*A*) Cancer-related defect before cranial bone grafting. (*B*) Improved contour gained by a cranial bone graft. (*Adapted from* Marx RE, Stern D. Oral and maxillofacial pathology: a rationale for diagnosis and treatment. Hanover Park (IL): Quintessence; 2002. p. 819; with permission.)

Fig. 22. A nonvascularized block bone graft often results in a deficient volume and resorption, particularly in the center, because the new bone formation arises mainly via osteoconduction from each bone margin.

consists of osteoid that unites the graft to the host bone and then undergoes a gradual resorption and replacement by new bone, which remodels the callus into a mature bony union.

Autogenous cancellous cellular marrow graft healing

Autogenous cancellous cellular marrow grafts are the most common grafts used by oral and maxillofacial surgeons and represent the most predictable outcome. Their value resides in the transplantation of more endosteal osteoblasts and marrow stem cells (osteocompetent cells) than any other graft. Their mechanism of healing—whether used in a maxillary alveolar cleft, a sinus augmentation, or a continuity defect of the mandible—is the same. It begins with the initial survival of the transplanted osteocompetent cells. These cells are open to the local environment and survive by oxygen and nutritional diffusion (plasmatic circulation) until the graft becomes revascularized by capillary ingrowth. Mature osteocytes do not survive the transplantation. Their mineral matrix is resorbed later when revascularization allows osteoclasts to enter the area.

Fig. 23. Microvascular fibulas represent a poor mandibular reconstruction because they are too small and too straight.

In the first week of a cancellous cellular marrow graft, platelets regulate the bone regeneration by their degranulation and secretion of seven growth factors: the three isomeres of platelet-derived growth factor (PDGFaa, PDGFbb, PDGFab), transforming growth factor-beta 1 and 2, vascular endothelial growth factor, and epithelial growth factor (Fig. 24). These growth factors are chemotactic, mitogenic, and angiogenic. As early as the third day, capillaries are seen to penetrate into the graft and the osteocompetent cells are seen to undergo a proliferation. By the seventh day, the platelets are exhausted and contribute little more to healing but are replaced by the macrophage, which was attracted to the graft by its initial hypoxic state and the chemoattraction from the platelet effects. The macrophage continues to secrete the same or similar growth factors until the graft is fully revascularized, which occurs between 14 and 21 days.

Once the graft begins revascularization—especially when it is completed—the oxygen and nutrients it affords allows the osteocompetent cells to synthesize and secrete osteoid. This process begins at approximately 2 weeks and continues to approximately 6 to 8 weeks. Once such revascularization occurs, osteoclasts arrive from the circulation and resorb the original mineral matrix and liberate BMP and IGF-1 and -2, which begins the maturation of the graft. As the osteoid is resorbed and new osteoblasts are induced, the newly forming bone is under function. The new bone is formed in accordance with this function and tends to be less cellular and more mineral and contains lamellar architecture (Fig. 25). This process continues from approximately the sixth week throughout the lifetime of the graft but is 90% mature by 6 months. The first 2 weeks of a cancellous cellular marrow graft involve cytokine secretion and intense cellular proliferation. The period from week 2 to week 8 involves osteoid formation. The period after 8 weeks is one of resorption—new bone apposition remodeling into a mature more mineralized bone (Fig. 26).

The clinical relevance of this mechanism of healing of each graft type relates to the general choice and expectation of the graft. Nonvascularized onlay block grafts from the ilium should be oversized to compensate for their expected volume reduction of up to 30%. Although they can be used successfully to reconstruct smaller continuity defects, they are best limited to defects 3 cm or smaller in younger, nonradiated patients in whom

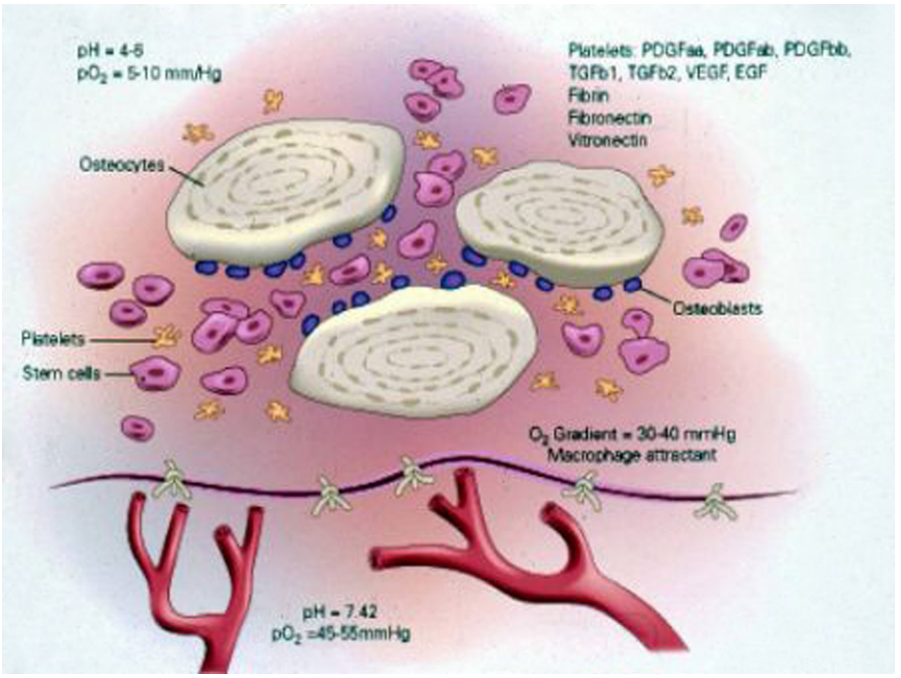

Fig. 24. A cancellous cellular marrow graft is directed by the growth factors from platelets initially then by macrophages, which cause capillary ingrowth and osteoprogenitor cell proliferation.

sufficient osteocompetent cells remain in the host bone or periosteum to bridge the defect by osteoconduction. Nonvascularized calvarial grafts are well suited for orbital, nasal, maxillary, and mandibular onlay grafts because of their embryologic similarity, which seems to confer a lesser volume reduction than other donor sites, and to their contour similarity. The amount of donor bone is limited and mostly cortical, however, which makes this site impractical for continuity defects, many sinus augmentations, and most alveolar clefts.

Vascularized block grafts are reasonable as an immediate stabilization graft to restore continuity and facial form. Their inadequate size and lack of morphologic similarity to the jaws makes them unsuitable for a definitive mandibular reconstruction, however. Cancellous cellular marrow grafts are best used in larger defects and in situations in which their particulate nature can be contained, such as alveolar clefts, sinus augmentations, and continuity defects. Their advantages are that they

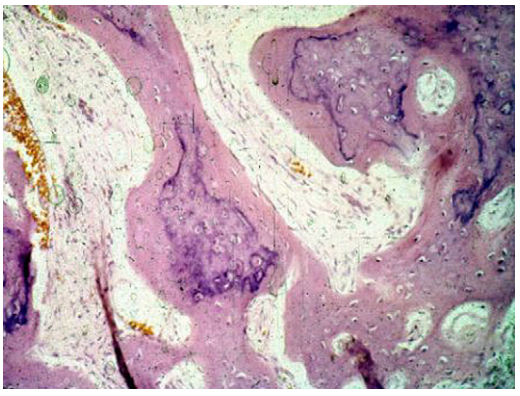

Fig. 25. Once a cancellous cellular graft becomes revascularized, osteoid is synthesized which then remodels into mature bone.

Fig. 26. The outcomes of cancellous cellular marrow grafts provide the best results related to bone height, width, and functional ability.

can be sculpted into a more ideal jaw contour, height, and width and have the least dimensional change. The bone that regenerates is active remodeling bone that responds well to functional loading. They readily support denture wearing and rehabilitation with dental implants.

Summary

Modern oral and maxillofacial surgeons are well advised to learn the details of skeletal embryology, bone physiology, bone structure, and different bone graft healing mechanisms. This knowledge will help clinicians to understand the numerous bone pathologies that require treatment and make the best selection of grafting approaches for each patient's needs.

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